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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Vernet t. al.
SERIAL NUMBER: 09/800,198 EXAMINER: Fozia M. Hamud
FILING DATE: March 5. 2001 ART UNIT: 1647
FOR: NOVEL PROTEINS AND NUCLEIC ACIDS ENCODING SAME

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

I, Dr. Seth Ettenberg hereby declare and state as follows:

1. I am employed by CuraGen, Inc., the assignee of this application. My title is Senior Research Scientist. I received a Ph.D. in Molecular Cell Biology in 2001 from the Uniform Services University of Health Science. I was a post-doctoral fellow in the laboratory of Dr. Stan Lipkowitz at the National Institutes of Health, National Cancer Institute, Genetics Branch, in Bethesda, MD from 2001-2002.

2. I have read, and am familiar with, the contents of the United States Patent Application entitled "Novel Proteins And Nucleic Acids Encoding Same", serial number 09/800,198, which was filed March 5, 2001. I understand that the pending claims are directed to an isolated polypeptide comprising SEQ ID NO:8.

3. I am aware that the Examiner has issued an Office Action. In particular, I understand that the Examiner has rejected the pending claims under 35 U.S.C. §§ 101 and 112, contending that the pending claims are not supported by either a specific and substantial asserted utility or a well-established utility.

4. I make this declaration to rebut the Examiner's assertion, with which I do not agree. It is my belief and professional scientific determination that the claimed compositions have a specific and substantial utility due to the following facts.

5. I have performed scientific experiments, or have had them performed under my supervision which successfully raised monoclonal antibodies to the polypeptide of SEQ ID NO:8. Fully human IgG1 monoclonal antibodies specific for SEQ ID NO:8 were produced through use of XenoMouse® technology (Yang et al., Cancer Res 1999 59:1236-43). Essentially, XenoMouse™ mice were immunized with polypeptide SEQ ID NO:8 or fragments thereof, lymphatic cells (such as B-cells) were recovered from the mice that express antibodies, recovered cells were fused with a myeloid-type cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines were screened and selected to identify hybridoma cell lines that produced antibodies specific to polypeptide SEQ ID NO:8.

6. The polypeptide SEQ ID NO:8 was detected in various cancer cell lines using the human monoclonal antibody specific for SEQ ID NO:8. Briefly, FACS analysis was performed on various cell lines selected based upon gene expression results (both positive and negative) from RTQ-PCR. Cell lines lacking expression of SEQ ID NO:8 (by RTQ-PCR) served as negative controls. Cells were washed with Ca and Mg-free 1X PBS (Media Tech, MT 21-040-CV). Versene (Invitrogen 15040-066) was added and the cells incubated at 37°C until they detached. Cells were counted and 500,000 to 1,000,000 cells/tube were used for FACS analysis. Cells were washed twice with ice-cold FACS buffer (1X PBS, 4% FBS) and resuspended in 1 μg of monoclonal antisera. Cells were mixed and incubated at 4°C or on ice for 30 min. Cells incubated with irrelevant monoclonal antisera served as additional negative controls. Cells incubated with anti-EGFR antibody served as positive controls. After

incubation, cells were washed twice with 1 mL ice-cold FACs buffer and then PE (R-Phycocrythin)-conjugated AffiniPure F(ab')2 secondary reagent was added. Cells were incubated at 4°C or on ice for 30 min, washed twice with 1 mL ice-cold FACS buffer and fixed with 400-500 mL 1% formaldehyde in PBS (Sigma F 1635). Cells were analysed using a Becton Dickinson FACSCalibur, detecting the PE Absorbtion/Emission spectra of 490/580.

7. The results of these studies are shown in Table 1, attached. Polypeptide SEQ ID NO:8 was detected in glioma (U251 and SNB-19), renal (786-0 and RXF393), and lung (HOP62) cancer cell lines that were shown to express the gene encoding SEQ ID NO:8 by RTQ-PCR analysis. Polypeptide SEQ ID NO:8 was not detected in prostate (PC3) which also does not express the gene encoding SEQ ID NO:8.

8. It is my belief that these results show that polypeptide SEQ ID NO:8 has utility as a specific marker that can be detected at least in glioma, renal and lung cancers.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18, United States Code, and that willful false statements may jeopardize the validity of this application and any patent issuing therefrom.

Dr Seth Ettenberg

Signed at New Haven, CT
this 16th day of October, 2003

TABLE 1. FACS analysis of cancer cell lines.

Cell Line	Type	RTQ-PCR results CT	GeoMean Neg Control	GeoMean Irelivant Antisera	GeoMean SEQ ID NO:8 Antisera	GeoMean EGFR pos control
U251	Glioma	26	3.05	11.19	369.02	236.09
SNB-19	Glioma	25	5.22	17.39	282.54	96.89
OVCAR5	Ovarian	26	5.24	6.67	8.71	94.61
786-0	Renal	29	3.37	4.71	18.74	202.31
PC3	Prostate	40	1.98	3.37	3.74	65.61
OVCAR3	Ovarian	40	2.73	5.52	6.39	185.43
IGROV1	Ovarian	40	3.59	5.48	5.30	63.70
HOP62	NSCL	29	5.17	11.50	31.46	78.68
RXF393	Renal	27	6.25	8.20	59.38	49.52
NCI-H82	SCLC	30	3.71	16.40	16.12	4.10
HCT-15	Colon	40	5.57	16.88	18.68	184.89
MDA-MB-468	Breast	40	5.07	6.92	8.23	585.21

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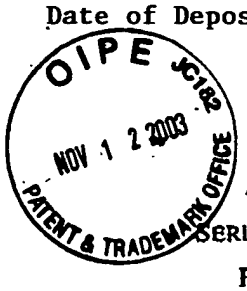

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DECLARATION UNDER 37 C.F.R. § 1.132

I, Xiaojia (Sasha) Guo, hereby declare and state as follows:

1. I am employed by Curagen Corporation, the assignee of this application. My title is Senior Research Scientist. I received a Ph.D. in Cell and Developmental Biology from Rutgers, the State University of New Jersey, where I studied the gene regulation of osteopontin. My post doctoral studies encompassed retinoids in cancer therapy at Cornell University Medical College, NY, NY. I have been employed at CuraGen since October, 2000.

2. I have read, and am familiar with, the contents of the United States Patent Application entitled "Novel Proteins And Nucleic Acids Encoding Same", serial number 09/800,198, which was filed March 5, 2001. I understand that the pending claims are directed to an isolated polypeptide comprising SEQ ID NO:8.

3. I am aware that the Examiner has issued an Office Action. In particular, I understand that the Examiner has rejected the pending claims under 35 U.S.C. §§ 101 and 112, contending that the pending claims are not supported by either a specific and substantial asserted utility or a well-established utility.

4. I make this declaration to rebut the Examiner's assertion, with which I do not agree. It is my belief and professional scientific determination that the claimed compositions have a specific and substantial utility due to the following facts.

5. I have performed, or have had performed under my supervision, scientific studies evaluating the quantitative expression and sequence homology of the nucleic acid (10129612.0.405) encoding the claimed polypeptide of SEQ ID NO:8 in tissue culture cells and in isolated normal and pathological human tissues.

6. Gene expression was consistently detected in a certain cancer specimens throughout these studies. Specifically, the gene was expressed in brain cancer (astrocytoma and glioma), renal, ovarian, melanoma cell lines in Panels 1 and 1.1. Panel 3D shows expression in additional glioma and a fibrosarcoma cell lines. Clinical specimens of ovarian, lung, kidney, liver, breast and bladder cancers express this gene as seen in Panels 2.2 and 2D. Therefore expression of this gene can be used to differentiate these pathological cells and tissues from normal tissue and as a diagnostic marker for the presence of these cancers.

7. The results of these studies demonstrate that the nucleic acid and the encoded claimed polypeptide of SEQ ID NO:8 are useful at least in detection, differentiation and therefore diagnostic applications in cancer. Thus, it is my opinion and belief that the Examiner should withdraw the rejection and allow the pending claims.

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to

be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18, United States Code, and that willful false statements may jeopardize the validity of this application and any patent issuing therefrom.

Dr. Sasha Guo

Signed at New Haven, CT
this 16 day of October, 2003